Review

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The role of ADAM17 during liver damage

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Abstract: A disintegrin and metalloprotease (ADAM) 17 is a membrane bound protease, involved in the cleavage and thus regulation of various membrane proteins, which are critical during liver injury. Among ADAM17 substrates are tumor necrosis factor α (TNFα), tumor necrosis factor receptor 1 and 2 (TNFR1, TNFR2), the epidermal growth factor receptor (EGFR) ligands amphiregulin (AR) and heparin-binding-EGF-like growth factor (HB-EGF), the interleukin-6 receptor (IL-6R) and the receptor for a hepatocyte growth factor (HGF), c-Met. TNFα and its binding receptors can promote liver injury by inducing apoptosis and necroptosis in liver cells. Consistently, hepatocyte specific deletion of ADAM17 resulted in increased liver cell damage following CD95 stimulation. IL-6 trans-signaling is critical for liver regeneration and can alleviate liver damage. EGFR ligands can prevent liver damage and deletion of amphiregulin and HB-EGF can result in increased hepatocyte death and reduced proliferation. All of which indicates that ADAM17 has a central role in liver injury and recovery from it. Furthermore, inactive rhomboid proteins (iRhom) are involved in the trafficking and maturation of ADAM17 and have been linked to liver damage. Taken together, ADAM17 can contribute in a complex way to liver damage and injury.

Keywords: ADAM17; IL-6; iRhom; liver damage; regeneration; TNF.

Introduction

Chronic liver disease and liver damage are a major public health challenge, accounting for more than 1 million deaths worldwide annually (Byass 2014; Koyama and Brenner 2017). Caused by viral infections, alcoholic and non-alcoholic liver disease, as well as auto-immune diseases affecting the liver or bile duct, hepatic inflammation and injury can result in liver fibrosis, cirrhosis, and even hepatocellular carcinoma (Byass 2014; Iwaisako et al. 2014; Koyama and Brenner 2017). Tissue damage can cause further immune activation, which can substantially promote liver inflammation, liver damage, and the development of pathologic changes such as liver fibrosis (Heymann and Tacke 2016; Robinson et al. 2016). Several cell death receptors have been associated with liver damage during liver disease (Luedde et al. 2014).

A disintegrin and metalloprotease 17 is a membrane bound protease, which cleaves membrane proteins to shed them from the plasma membrane (Lambrecht et al. 2018; Zunke and Rose-John 2017). Originally, ADAM17 was identified through its role in the proteolytic cleavage of membrane bound TNFα (Kriegler et al. 1988; Mohler et al. 1994), and named TNFα converting enzyme (TACE) (Black et al. 1997; Moss et al. 1997). Proteolytic cleavage by ADAM17 is involved in modulating several important signaling pathways, which also have been shown to play an important role in liver regeneration acting as mitogens for hepatocytes (Berasain et al. 2005a; Kiso et al. 2003; Michalopoulos 2007; Mitchell et al. 2005; Zarnegar et al. 1991). This review will focus on the role of ADAM17, its regulation, and ADAM17 dependent pathways during liver damage.

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ADAM17 protease

ADAM17 is comprised of an N-terminal signal peptide followed by a pro-domain, the metalloproteinase domain and a disintegrin-like domain, a cysteine-rich membrane proximal domain (MPD), and a unique Conserved Adam 17 Dynamic Interaction Sequence (CANDIS) region, succeeded by the stalk region, transmembrane helix and intracellular cytosolic tail (Düsterhöft et al. 2019). ADAM17 and ADAM10, which is closest to ADAM17 in structure and function, are atypical members of the ADAM family, as they contain the MPD region, instead of the cysteine-rich and EGF-like domain found in other ADAM family proteins (Takeda 2009). The MPD region and the CANDIS, which is not found in ADAM10, have been reported to be involved in the dimerization of ADAM17, while the CANDIS region has further been suggested to facilitate the interaction of ADAM17 with specific substrates, such as IL-6R (Düsterhöft et al. 2014; Riethmueller et al. 2016). Notably, in contrast to ADAM10, ADAM17 is not constitutively active, and multiple additional mechanisms for how ADAM17 activity is regulated have been brought forward (Grötzinger et al. 2017).

While ADAM17 transcription can be induced by inflammation and in neoplastic tissue, systemic over-expression was not found to result in upregulated levels of substrate shedding *in vivo* (Düsterhöft et al. 2019; Yoda et al. 2013). This indicated that ADAM17's proteolytic activity is regulated at the post-transcriptional level (Armstrong et al. 2006; Kornfeld et al. 2011; Ringel et al. 2006; Rzymski et al. 2012; Satoh et al. 2004, 2008). A detailed overview of ADAM17 activity, regulation and substrates is given elsewhere (Zunke and Rose-John 2017). Briefly, after ADAM17 is synthesized in the endoplasmic reticulum (ER), it requires various modifications before it becomes catalytically active. Activation of ADAM17 is mediated by cleavage of the pro-domain by furin-like proprotein convertases in the Golgi (Endres et al. 2003; Schlondorff et al. 2000; Wong et al. 2015) and phosphorylation of its cytosolic tail, relieving dimerization inhibition of ADAM17, via the ERK1/2 and p38 MAPK pathways (Figure 1) (Fan and Derynck 1999; Fan et al. 2003; Gechtman et al. 1999; Killock and Ivetic 2010; Lemjabbar-Alaoui et al. 2011; Saad et al. 2019; Schwarz et al. 2014; Xu and Derynck 2010). In the ER, the pro-protein is suggested to act as a chaperone for ADAM17, ensuring correct folding and processing, while protecting ADAM17 from degradation (Milla et al. 1999). In addition to this, the pro-protein has been reported to contribute to active site inhibition of ADAM17. Thus, cleavage of the pro-protein is important to release the inhibition of the catalytic site (Milla et al. 1999). Hence, the processing of ADAM17 has been suggested to contribute to its activity following phorbol 12-myristate 13-acetate (PMA) stimulation (Nagano et al. 2004; Soond et al. 2005). However, the absence of the cytoplasmic tail is dispensable for PMA mediated ADAM17 activation (Horiuchi et al. 2007b; Reddy et al. 2000). Consistently, rapid ADAM17 response following physiological stimuli requires its transmembrane domain, but not its cytoplasmic tail (Le Gall et al. 2010).

Additionally, the disintegrin domain has been suggested to play a role in the conformation of the ADAM17 protein, acting as a scaffold ensuring the C-shaped conformation and bridging between the catalytic and the MDP domain (Takeda et al. 2006). This may play a role in substrate

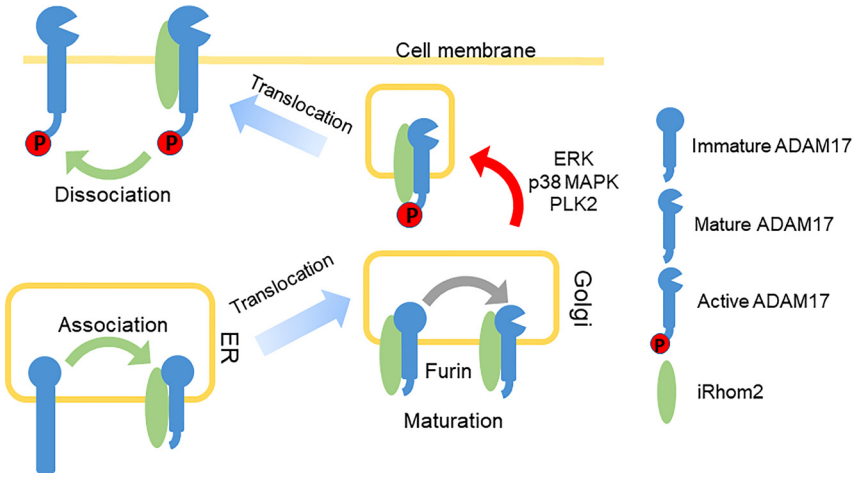

Figure 1: Schematic representation of the ADAM17 trafficking.
A simplified schematic illustrating that iRhom2 creates a stable complex with ADAM17 in the Endoplasmic Reticulum, which leads to translocation of the complex to the Golgi apparatus and maturation of ADAM17 by removing the pro-domain by furin-like proprotein convertases. The mature form consists of a metalloprotease domain and cytosolic tail, which is next phosphorylated by several kinases, like ERK1/2, p38 MAPK and PLK2. The complex translocates to the cell membrane, where iRhom2 can dissociate from ADAM17.

binding. Protein disulphide isomerase (PDI) has been demonstrated to inactivate ADAM17, by changing the conformation of the MDP region of ADAM17 from an open to a closed conformation (Düsterhöft et al. 2013, 2014; Lorenzen et al. 2012). In addition, this has also been suggested to affect the shedding activity of ADAM17, as only the open form of MDP binds to phospholipid phosphatidylserines, which are translocated to the outer leaflet of the cell membrane by scramblases in response to stimulation with PMA, for example. This interaction between phospholipid phosphatidylserines and open form MDP has been reported to result in a conformational change, which may contribute to the initialization of the shedding activity (Sommer et al. 2016a,b). Likewise, the CANDIS region has also been suggested to contribute to the conformational change in ADAM17 activating its shedding activity. The CANDIS region has been reported to contain an amphipathic helix, whose interaction with the cell membrane is enhanced in the presence of phosphatidylserine. High cholesterol in the cell membrane, on the other hand, has been found to counteract this interaction, thus indicating that cell membrane composition may be involved in the regulation of ADAM17 activity (Düsterhöft et al. 2015; Schütze et al. 2003; Tellier et al. 2006).

Dimerization of ADAM17 with α5β1 integrin via its disintegrin domain has been suggested to promote the binding of active site tissue inhibitor of metalloproteinase 3 (TIMP3) (Wisniewska et al. 2008), while decreasing the accessibility of the active site by steric hindrance (Bax et al. 2004; Huang et al. 2005). In addition to their role in trafficking ADAM17 from the ER to the Golgi, iRhoms have been demonstrated to play a role in the regulation of ADAM17 activation at the cell membrane, with ERK1/2-dependent phosphorylation of the cytoplasmic iRhom2 resulting in the release of mature ADAM17 and increased ADAM17 mediated shedding of TNFα (Adrain et al. 2012; Grieve et al. 2017; Maney et al. 2015).

Notably, ADAM17 deficient mice are perinatally lethal, exhibiting a specific developmental phenotype relating to epidermal growth factor receptor (EGFR) signaling (Peschon et al. 1998). These and other signaling pathways are modulated by ADAM17's proteolytic activity during liver damage (Figure 2).

ADAM17 during liver damage

ADAM17 deficient mice are perinatally lethal exhibiting development defects in the eye, hair and skin, which are associated with defects in transforming growth factor alpha (TGFα) shedding (Peschon et al. 1998). However, the development of a hypomorph mouse model system, in which *Adam17* mRNA and protein levels are highly reduced, showed a critical role of ADAM17 in intestinal barrier function while mice were viable (Chalaris et al. 2010). Moreover, the generation of conditional ADAM17 knockout mice showed that myeloid specific deletion resulted in the protection of mice against LPS induced septic shock, with reduced serum TNFα levels following the challenge

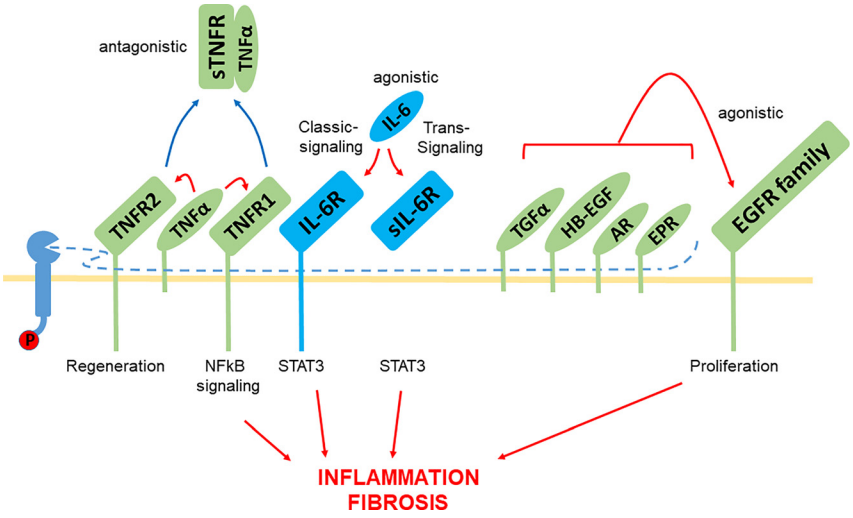

Figure 2: Schematic representation of the ADAM17 enzymatic activities.
A simplified schematic illustrates that ADAM17 can shed substrates from the cell surface, thereby controlling pro-inflammatory and proliferation pathways. Specifically, TNFα binds to TNFR1, which leads to activation of NF-κB and Jak2/STAT3 pathways respectively, whereas cleaving the receptors from the cell membrane can result in limited signaling. Other substrates include growth factors like TGFα, heparin-binding EGF, amphiregulin, and epiregulin, which can bind to EGFR and induce proliferation. Shedding of IL-6R can result in IL-6 trans-signaling via gp130.

(Horiuchi et al. 2007a). Both, specific deletion of ADAM17 in either myeloid cells or hepatocytes resulted in reduced serum TNFα levels following stimulation with LPS and partial hepatectomy although liver regeneration appeared normal in these settings (McMahan et al. 2013). In turn, hepatocyte specific deletion of ADAM17 resulted in increased liver cell death following injection with anti-Fas antibodies, attributed to reduced TNFR1 and EGFR ligand shedding (Murthy et al. 2010). Consistently, the absence of TNFR1 reduced CD95 induced apoptosis in this setting (Murthy et al. 2010). Furthermore, adenoviral mediated expression of ADAM17 prevented liver cell damage during acetaminophen induced toxicity (Murthy et al. 2010). In turn, treatment of mice with α-1 antitrypsin (AAT) showed increased survival following CD95 stimulation, which coincided with reduced activity of ADAM17 and decreased serum levels of TNFα. Consistently, AAT treatment resulted in protection from liver failure following acetaminophen induced liver toxicity (Jedicke et al. 2014). These data suggest that there are overlapping functions of ADAM17.

ADAM17 maturation is triggered by co-factors such as iRhoms, which are inactive members of the rhomboid protease family (Al-Salihi and Lang 2020). The founding member rhomboid-1 was identified in *Drosophila* as a Golgi protein, which cleaves the EGF like ligand *spitz*, promoting its secretion (Lee et al. 2001; Urban et al. 2001). However, rhomboid proteins exist, which lack catalytic residues and are descriptively named inactive rhomboids (iRhom). There are two iRhom proteins in humans and mice, named iRhom1 and iRhom2, whereas in *Drosophila* there is only one iRhom member (Lemberg and Freeman 2007). IRhoms are unable to cleave traditional rhomboid substrates and iRhom deficient flies exhibit an extended sleep cycle, which has been associated with enhanced EGF receptor signaling (Zettl et al. 2011). While the single iRhom found in *Drosophila* induces ER associated ligand degradation (ERAD) and subsequent inhibition of EGFR signaling, both iRhom1 and iRhom2 have been shown to interact with ADAM17 (Li et al. 2015; Zettl et al. 2011). Deletion of both, iRhom1 and iRhom2 resembles the phenotype observed in ADAM17 deficient mice (Li et al. 2015). Moreover, examination of newborn iRhom 1 and 2 double knockout out mice, demonstrated a significant lack of mature ADAM17 in multiple tissues examined, including the liver. Notably, mature ADAM17 expression was also found to be significantly reduced in livers of iRhom2 knockout mice (Li et al. 2015). In turn, iRhom1 and iRhom2 single knockout mice are viable and fertile (Adrain et al. 2012; Li et al. 2015; McIlwain et al. 2012; Siggs et al. 2012). These data suggest that iRhom1 and iRhom2 promote ADAM17 maturation in different compartments, which allows single knockout mice to overcome the severe phenotypes observed in ADAM17 deficient mice (Peschon et al. 1998). In addition to ADAM17 activation, iRhom proteins may play a role in substrate specificity of ADAM17 (Maretzky et al. 2013). In mouse embryonic fibroblasts (MEF) iRhom2 triggers, among others, shedding of the EGFR ligands HB-RGF, Amphiregulin, Epiregulin, but not TGFα (Maretzky et al. 2013). IRhoms can also regulate ADAM17 activation via their cytoplasmic tail. Deletion of the cytoplasmic tail results in increased ADAM17 activity and TNFR shedding, which triggers resistance to TNF mediated cell death (Maney et al. 2015). The mouse curly bare (*cub*) mutation, which deletes most of the cytoplasmic domain of iRhom2 showed alterations in EGFR signaling (Hosur et al. 2014; Siggs et al. 2014). Consistently, iRhom2 gain of function mutations in its N-terminal cytoplasmic tail, identified in the inherited Tylosis with oesophageal cancer (TOC) syndrome, result in increased EGFR ligand and TNFR1 shedding (Blaydon et al. 2012; Brooke et al. 2014; Maney et al. 2015; Saarinen et al. 2012). Dissociation of iRhom2 from ADAM17 takes place after phosphorylation of the cytoplasmic tail of iRhom2, which can occur at three different sites. Point mutations in each site downregulated the activity of ADAM17, while additive mutations resulted in complete loss of ADAM17 mediated shedding (Cavadas et al. 2017; Grieve et al. 2017). Moreover, co-immunoprecipitation of the extracellular iRhom2 domain in MEFs upon stimulation with PMA demonstrated reduced interaction with ADAM17 compared to unstimulated cells. Grieve et al. concluded that phosphorylation of iRhom2 on the cell membrane results in the dissociation from ADAM17 followed by increased catalytic activity (Grieve et al. 2017).

The regulation of ADAM17 via the interaction with iRhom2 has been suggested to play a significant role in liver disease. Absence of iRhom2 resulted in impaired shedding of TNFα and consequently reduced susceptibility towards LPS mediated liver damage and septic shock (McIlwain et al. 2012). Moreover, iRhom2 was significantly upregulated following exposure to a mixture of air pollutants (PM2.5), which was accompanied by augmented levels of TNFR2, ADAM17 and TNFα, hepatic steatosis, and dyslipidemia in the livers of WT mice. Markedly, however, PM2.5-induced liver damage and dyslipidemia were attenuated in the absence of iRhom2, while TNFα expression, as well as the expression of associated pro-inflammatory cytokines, were reduced *in vitro* (Ge et al. 2017). Moreover, mature ADAM17 expression and TNFR shedding is increased during bile duct ligation (BDL), a murine liver fibrosis model system (Sundaram et al. 2019). The absence of iRhom2 resulted in decreased ADAM17 activation and reduced shedding of TNFRs following BDL. Consequently, hepatic stellate cell proliferation and liver fibrosis was increased in *iRhom2*$^{-/-}$ mice following BDL (Sundaram et al. 2019). Notably, myeloid and hepatocyte specific deletions of ADAM17 have

also been associated with decreased TNFα serum levels and reduced TNFR1 shedding (McMahan et al. 2013; Murthy et al. 2010). Moreover, ursodeoxycholic acid (UDCA), used as a therapeutic agent for primary biliary cirrhosis and intrahepatic cholestasis, has not only been associated with regulating the expression of inflammatory cytokines, including TNFα, but has also been demonstrated to improve BDL-induced cholestasis in mice by inhibiting ADAM17 activity and reducing sMet, with a similar trend for TNFα (Buryova et al. 2013; Ishizaki et al. 2008; Neuman et al. 2002). In addition, iRhom2 is a key regulator of inflammation driving non-alcoholic fatty liver disease (Xu et al. 2020). The absence of iRhom2 significantly alleviated insulin resistance, hepatic steatosis, and activation of inflammatory macrophages in iRhom2 knockout mice in response to high fat diet. This was associated with the interaction of hepatic iRhom2 with mitogen-activated protein kinase 7 (MAP3K7) and subsequent MAP3K7 phosphorylation, leading to NF-κB signaling and JNK/IRS1 signaling pathway activation, while impairing AKT/GSK3β-associated insulin signaling (Xu et al. 2020). Similarly, hepatocyte specific deletion of ADAM17 has been shown to improve liver steatosis in a mouse model of NAFLD/NASH (Casagrande et al. 2017). Taken together, ADAM17 dependent signaling is critical during liver damage and in liver disease (Table 1).

ADAM17-dependent pathways and their role during liver damage

TNFα signaling

TNFα is a central cytokine during liver damage (Koyama and Brenner 2017; Luedde et al. 2014). Named for its anti-tumor activity, it was originally identified in the late '70s and is the

Table 1: Overview of the ADAM17 dependent pathways on liver disease.

Liver diseases	Examples for relevant ADAM17-regulated processes	Reference studies
Liver fibrosis and cirrhosis	TNFα was associated with mediating NF-κB induced HSC activation, as well as promoting HSC survival, thereby contributing to liver fibrosis indirectly.	(Osawa et al. 2013; Pradere et al. 2013; Tarrats et al. 2011)
	Cleavage of MerTK, contributed to the activation of HSCs and promoted liver fibrosis in NASH.	(Cai et al. 2020)
	Amphiregulin induced fibrogenic activity of hepatic stellate cells and promoted liver fibrosis.	(Berasain et al. 2005b; McKee et al. 2015; Santamaria et al. 2019)
Hepatocellular carcinoma	TNF signaling via NF-κB was reported to have a protective, anti-apoptotic effect, which contributes to hepatocyte carcinogenesis.	(Schwabe and Brenner 2006)
	EGFR activation was shown to have a tumor-promoting role.	(Fuchs et al. 2014; Lanaya et al. 2014)
	Hepatic ADAM17 regulation by TIMP3 slowed tumorgenesis.	(Casagrande et al. 2017)
Alcoholic and non-alcoholic fatty liver disease (NAFLD) as well as non-alcoholic steatohepatitis (NASH)	Augmented levels of EGFR ligand amphiregulin was induced by fibrogenic activity of hepatic stellate cells, driving liver fibrosis.	(McKee et al. 2015)
	ADAM17-mediated cleavage of MerTK was demonstrated to contribute to the activation of HSCs, driving liver fibrosis in NASH.	(Cai et al. 2020)
	iRhom2 overexpressing mice showed inflammatory aggravation mediated by NF-κB activation, whereas in the ADAM17 KO model, mice had alleviated hepatic steatosis.	(Casagrande et al. 2017; Xu et al. 2020)
Viral hepatitis	TNFα was shown to be crucial to mounting an appropriate T-cell response to infection with hepatitis B virus.	(Beyer et al. 2016; Kasahara et al. 2003)
	TNFα was associated with increased cell death via suppression of NF-κB during viral infection.	(Park et al. 2012; Xu et al. 2014)
Liver regeneration	HGF and EGFR ligands, HB-EGF and amphiregulin acted as mitogens for hepatocytes during liver regeneration.	(Berasain et al. 2005a,b; Kiso et al. 2003; Mitchell et al. 2005; Takemura et al. 2013)
	IL-6 was shown to have a transignaling role in liver regeneration.	(Fazel Modares et al. 2019; Jin et al. 2006; Riethmueller et al. 2017)
	IL-6 was shown to have a role in maintaining the biliary tree in liver.	(Demetris et al. 2006; Nozaki et al. 2005)

founding member of a superfamily of cytokine-like molecules (Carswell et al. 1975; Green S Fau-Chiasson et al.). Along with their cognate receptors, the TNFR superfamily control signaling pathways in immunity and disease (Dostert et al. 2019; Kondylis and Pasparakis 2019). TNFα can induce signaling via two cognate receptors TNFR1 and TNFR2. TNFα has been shown to promote liver damage during toxic liver damage (Yin et al. 1999). Injection of TNFα can cause severe liver damage and septic shock when applied in combination with D-Galactosamine (D-Gal), which is dependent on TNFR1 (Luedde et al. 2014). Consistently, TNFR1 deficient mice are protected from liver injury and septic shock following lipopolysaccharide (LPS) challenge (Pfeffer et al. 1993; Rothe et al. 1993). TNFR1 is ubiquitously expressed and can be activated by both shed and membrane bound TNFα. TNFR2 on the other hand is expressed in a more limited fashion on immune, neuronal, cardiac, endothelial and stem cells and binds membrane bound TNFα with higher affinity (Dostert et al. 2019). Notably, ADAM17 can cleave membrane bound TNFα into its soluble form as well as the binding receptors TNFR1 and TNFR2 (Peschon et al. 1998). Accordingly, ADAM17 contributes to soluble TNFα's systemic effects. Conversely, shedding of the TNFRs reduces TNFR1 signaling, and resulting soluble TNFRs can bind to TNFα thereby reducing its biological activity. Therefore, depending on the balance of TNFα versus TNFR cleavage and the predominant cell on which this happens, ADAM17 can have opposite effects on liver damage and fibrosis. Furthermore, the TNF pathway once activated also has dual outcomes when it comes to hepatocyte death and proliferation.

The binding of TNFα to TNFR1 results in a conformational change exposing the death domain of TNFR1. This leads to the recruitment of the adaptor protein TNFR1-associated death domain (TRADD) via the interaction of the death domains. The interaction of TNFR1 and TRADD provides an assembly scaffold for the recruitment of further adaptor molecules, resulting in the formation of complexes I and II and subsequent induction of TNF signaling. Complex I consists primarily of the receptor itself, the adaptor protein TRADD, TNFR-associated factor 2 (TRAF-2), cellular inhibitors of apoptosis 1 and 2 (cIAP1/2), linear ubiquitin chain assembly complex (LUBAC) and receptor-interacting serine/threonine-protein kinase 1 (RIPK1). Complex II is comprised of three distinct, Fas-associated death domain (FADD) and long isoform of FLICE-like inhibitory protein ($FLIP_L$) containing sub complexes, IIa-c. Phosphorylation, ubiquitination and de-ubiquitination of RIPK1 controls whether TNFα binding to TNFR1 results in signaling via complex I or complex II (Feoktistova et al. 2011; Wang et al. 2008; Yu and Cleveland 2018). The TNFα-TNFR1 signaling pathway can induce several different cellular responses including inflammation, apoptosis and necrosis by activating gene transcription in downstream signaling pathways such as NF-κB, JNK, and p38.

Complex I activates downstream NF-κB signaling resulting in the expression of pro-inflammatory and pro-survival genes (Dostert et al. 2019; Hsu et al. 1995, 1996; Kondylis and Pasparakis 2019; Ting et al. 1996). In turn, NF-κB inhibition and complex II formation results in cell death and induces tumor regression (Dostert et al. 2019; Fulda 2015; Kondylis and Pasparakis 2019; Xie et al. 2016). The mode of cell death induced depends on which type of complex II is formed and the presence or absence of active caspase 8. In complex II $FLIP_L$ mirrors caspase 8 and is catalytically inactive, but forms catalytically active heterodimers, which have a reduced activity and altered targets compared to caspase 8 homodimers (Dostert et al. 2019; Pop et al. 2011). While the short isoforms (S and R) bind to caspase 8 and inhibit its activation (Golks et al. 2005; Irmler et al. 1997). Complexes IIa and IIb induce apoptosis, are caspase 8 dependent and contain either TRADD or RIPK1 respectively. Absence of active caspase 8 results in necroptosis (Holler et al. 2000; Vercammen et al. 1998; Zhang et al. 2009). Caspase 8 is an initiator caspase; when active, it triggers a downstream cascade of caspase cleavage, leading to activation of effector caspases such as caspase 3, ultimately leading to apoptosis (Dostert et al. 2019; Stennicke et al. 1998). Consistently, TNFα expression levels correlate with active caspase 3 in patient cohorts suffering from hepatitis C virus infection, which can increase the sensitivity towards TNFα mediated cell death (Park et al. 2012; Walsh et al. 2004). TNFα promotes chronic viral infection and hepatitis in murine viral infection model systems (Beyer et al. 2016; Suresh et al. 2005; Xu et al. 2014; Zhuang et al. 2020), and Hepatitis B virus infection sensitizes hepatocytes towards TNFα mediated cell death (Jia et al. 2015). In contrast to Complexes IIa and IIb, Complex IIc, also known as the necrosome, depends on RIPK1, 3 and mixed lineage kinase domain-like (MLKL) to induce necroptosis via the insertion of MLKL into the plasma membrane creating an ion channel (Cai et al. 2014; Dostert et al. 2019; Galluzzi et al. 2014; Kondylis and Pasparakis 2019; Wang et al. 2008, 2014; Weber et al. 2018). Notably, complex II formation can occur independently of its role in cell death and inflammation. This last has been linked to chromosomal stability, suggesting a possible mechanism relating loss of caspase 8 to hepatocellular carcinoma (HCC) among other cancers (Liccardi et al. 2019; Soung et al. 2005).

During liver fibrosis, TNFα produced by Kupffer cells and neutrophils induces Hepatic stellate cell (HSC) activation and proliferation. Specifically, TNFα and LPS

promote proliferation and survival of HSCs by activating NF-κB and down-regulating pro-apoptotic genes (Gandhi 2017; Osawa et al. 2013; Seki et al. 2007). Accordingly, liver damage and fibrosis were decreased in TNFR1 KO mice and TNFR1&2 double knockout mice compared to wild-type or single TNFR2 KO mice in a murine model system of fibrosis, suggesting TNF-TNFR1 but not TNFR2 is critical for HSC activation and liver fibrosis (Tarrats et al. 2011).

IL-6 receptor signaling

IL-6 signaling is induced by IL-6, secreted during the inflammatory response, binding to its non-signal transducing α-receptor IL-6R and the signaling receptor gp130 (Tanaka et al. 2014). IL-6 signaling can also be induced in cells lacking membrane bound IL-6R, albeit IL-6 cannot bind to gp130 in the absence of IL-6R. However, IL-6 cannot bind to gp130 on its own, but rather gp130 binds the IL-6/IL-6R complex (Schmidt-Arras and Rose-John 2016). This signaling requires the shedding of membrane bound IL-6R. Active ADAM17 and ADAM10 can cleave IL-6R, resulting in soluble IL-6R (sIL-6R) (Müllberg et al. 1993; Riethmueller et al. 2017). Accordingly, sIL-6R can still bind IL-6 and gp130 on cells, which lack IL-6R, and induce gp130 mediated signaling, so-called IL-6 trans-signaling (Mackiewicz et al. 1992). IL-6 expression during the inflammatory response to injury, results in the induction of acute phase proteins such as C-reactive protein and fibrinogen. In the liver, IL-6, expressed by neutrophils, monocytes and macrophages, is a major force driving the expression of acute phase proteins (Schmidt-Arras and Rose-John 2016). Aside from its role prominent as a potent pro-inflammatory cytokine, IL-6 has been reported to play a critical role in liver regeneration. Hepatectomy in rats results in increased TNFα levels, succeeded by significantly increased IL-6 expression (Trautwein et al. 1996). Consistently, B cells and macrophages triggered IL-6 expression in mice following partial hepatectomy (Behnke et al. 2018). In the absence of IL-6 signaling tissue regeneration after partial hepatectomy was impaired (Cressman et al. 1996; Fazel Modares et al. 2019). Likewise, inhibition of IL-6 signaling resulted in increased liver damage in response to carbon tetrachloride (CCL_4) induced liver damage (Gewiese-Rabsch et al. 2010). Moreover, liver injury was exacerbated by inhibition of IL-6 signaling in a non-alcoholic steatohepatitis (NASH) model (Yamaguchi et al. 2011). The absence of gp130 – abolishing all IL-6-type cytokine signaling – resulted in increased liver damage following BDL, which was associated with increased bacterial burden (Wuestefeld et al. 2005). Moreover, lack of IL-6, gp130, and STAT3 signaling in the liver promoted establishment of steatohepatitis (Kroy et al. 2010).

While classical signaling via the membrane-bound IL-6 receptors is associated with the inflammatory role of IL-6, IL-6 trans-signaling has been suggested to play a major role in liver regeneration. Hyper-IL-6 is a fusion protein between IL-6 and soluble IL-6R, which stimulates trans-signaling in gp130 expressing cells (Schmidt-Arras and Rose-John 2016). Mice expressing Hyper-IL-6 exhibited hepatocellular hypertrophy and accelerated liver regeneration following partial hepatectomy (Peters et al. 2000). Consistently, in a mouse model exhibiting only IL-6 trans-signaling, liver regeneration following partial hepatectomy was comparable to control animals (Fazel Modares et al. 2019). Furthermore, administration of Hyper-IL-6 during toxic liver injury could alleviate liver damage and promote hepatocyte proliferation (Galun et al. 2000). Taken together, these findings suggest a prominent role of IL-6 trans-signaling, triggered by ADAM17 IL-6R cleavage, during liver regeneration. Reduced IL6-trans-signaling might result in increased liver damage and prolonged injury.

EGFR signaling

ADAM17 can cleave a variety of EGFR ligands including amphiregulin, heparin-binding-EGF-like growth factor, epiregulin, TGFα and epigene (Sahin and Blobel 2007; Sahin et al. 2004; Sigismund et al. 2018). Conditional deletion of EGFR on hepatocytes was associated with increased liver transaminases and reduced survival following partial hepatectomy (Natarajan et al. 2007). Consistently, mice with hepatic deletion of EGFR showed increased liver damage and cancer formation following DEN treatment (Lanaya et al. 2014). In turn, macrophage specific deletion of EGFR caused reduced cancer growth (Lanaya et al. 2014). Treatment with the EGFR inhibitor erlotimib alleviated the establishment of liver fibrosis and the development of hepatocellular carcinoma (Fuchs et al. 2014). In turn, ectodomain shedding of EGFR ligands and TNFR1 can critically regulate acute liver damage (Murthy et al. 2010). Conditional deletion of HB-EGF results in increased liver injury following acute toxic hepatitis (Takemura et al. 2013). Furthermore, overexpression of HB-EGF results in aggravated liver fibrosis following chronic liver injury (Guo et al. 2017). Deletion of amphiregulin prevented hepatocyte proliferation following partial hepatectomy. Furthermore, pretreatment with amphiregulin could prevent liver damage following CD95 stimulation (Berasain et al. 2005b). Consistently, amphiregulin deficient mice showed increased liver injury during bile duct ligation

(Santamaria et al. 2019). Collectively, these reports hint to a rather protective role of EGFR ligands and thus a potentially prominent role for ADAM17 shedding during liver injury but cell, substrate, and context specific effects might apply.

Other substrates

Likewise, the receptor for hepatocyte growth factor, c-Met has been reported to play a significant role in liver development and regeneration (Chalupský et al. 2013). Chalupský et al. demonstrate that ADAM17 along with ADAM10 are involved in releasing the soluble form of the c-Met receptor, sMet from the cell surface in human hepatocellular HepG2 and hepatic stellate cell LX2 lines, while postulating a dominant role for ADAM17. Moreover, serum levels of sMET in a hepatobiliary obstruction mouse model correlated with the level of hepatic injury, expression of established markers of liver damage including alanine aminotransferase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), and total bilirubin, as well as with subsequent regeneration (Chalupský et al. 2013). Hepatocyte specific, post partum deletion of c-Met resulted in increased hepatocyte apoptosis and reduced proliferation following transfer experiments (Kaldenbach et al. 2012). Consistently, hepatocyte specific deletion of c-Met resulted in fulminant liver damage and lower hepatocyte proliferation following bile duct ligation (BDL) (Giebeler et al. 2009).

ADAM17 as a therapeutic target

Since its discovery as a protease involved in the activation of the TNF pathway, ADAM17 has been a focal point of research aiming to find new therapeutics for inflammatory diseases (Calligaris et al. 2021). However, due to its involvement in the regulation of multiple signaling pathways, with over 80 different substrates aside from TNF reported, and the similarity of its catalytic domain to ADAM10, which plays an important role in vascularisation, cell proliferation and differentiation, and several other metalloproteinases, targeting ADAM17 has proven difficult (Calligaris et al. 2021; Maskos et al. 1998; Riethmueller et al. 2016; Wetzel et al. 2017; Zunke and Rose-John 2017). Initial drugs designed to target ADAM17 activity demonstrated severe side effects, including serious hepatotoxicity, outweighing their therapeutic benefits (Calligaris et al. 2021; Moss et al. 2008; Rossello et al. 2016). Thus, the risk of deregulating numerous physiologically relevant processes and the broad expression of ADAM17 throughout the body, pose a caveat for targeting ADAM17 therapeutically (Calligaris et al. 2021; Zunke and Rose-John 2017). Nevertheless, several promising approaches have been explored recently and are reviewed in more detail by Calligaris et al. (2021). These include the use of more specific small molecules, manipulating the selectivity of endogenous inhibitors of ADAM17, as well as targeting the ancillary domains of ADAM17 or regulators, that are specific and essential for ADAM17 activation, such as iRhoms (Calligaris et al. 2021). For example, Wong et al. developed a stable form of the autoinhibitory pro-domain of ADAM17 (or TACE pro-domain), TPD, which demonstrated promising attenuation of ADAM17-mediated disease in models of sepsis, rheumatoid arthritis (RA) and inflammatory bowel disease as well as in RA patients (Wong et al. 2016).

Notably, targeting iRhom2 therapeutically is a particularly promising route: Not only is iRhom2 specific for ADAM17, but also it carries the advantage that, iRhom1 can substitute for the loss of iRhom2-mediated regulation of ADAM17. At the same time, using iRhom2 as a therapeutic target could regulate several pro-inflammatory ADAM17-mediated factors, including IL-6 signaling (Calligaris et al. 2021).

Concluding remarks

ADAM17 substrates play a critical role during liver damage in various model systems. Furthermore, data from conditional ADAM17 deficient mice corroborate the significance of ADAM17 during liver damage. Myeloid deletion of ADAM17 resulted in reduced soluble TNFα production. In turn, hepatocyte specific deletion resulted in increased liver damage resulting from reduced shedding of TNFRs. Furthermore, IL-6 trans-signaling is important for liver regeneration and hepatocyte proliferation. Accordingly, cell type specific regulation of ADAM17 is critical to orchestrating liver regeneration and liver damage. In addition, adaptor molecules such as iRhoms might cause cell specific or substrate specific ADAM17 activity and thus could critically regulate liver damage during disease model systems. However, further characterization of ADAM17 in different cell subsets is required to fully understand the complete picture of ADAM17 during liver damage and disease. This is particularly important to further explore ADAM17 or its regulators as a therapeutic target.

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